Remarks

Claims 1-10 and 23-24 stand rejected. Claims 11-14 appear to be free of all prior art and other formal rejections, although this is not stated in the Office Action.

The Rejection of Claim 10 under 35 U.S.C. § 112, first paragraph

Claim 10 is rejected as failing to comply with the enablement requirement. Two issues are raised under this rubric. First, the preamble ("method for distinguishing") was objected to as inapposite for the actual method steps. The preamble is now amended to reflect more accurately the purpose of the method ("method of detecting a malignant thyroid neoplasm"). Second, the method is objected to because "the number of likely false positive results is not a reasonable number. The Office Action asserts that "a substantial number of non-thyroid cancers including melanoma, colon carcinoma, head and neck cancers, and lung cancers exhibit the specified mutation." This objection is addressed in the accompanying Declaration Under Rule 132.

As detailed in the declaration, because the method of claim 10 is performed on humans suspected of having a thyroid neoplasm, *e.g.,* having a suspicious thyroid nodule, there is a significant selection and statistical tilting toward detection of thyroid cancers. Thus, even though other cancers may be associated with a comparably high rate of *BRAF* mutations in the general population, when one only looks among those humans who are suspected of having a thyroid neoplasm the likelihood of finding a thyroid neoplasm is very great. This limitation on the population to be tested skews the rates greatly in favor of detection of thyroid neoplasms, such that $\geq$ 95 % of the detected *BRAF* T1796A mutations should be due to thyroid cancers.

It is thus respectfully submitted that the number of false positives that the claimed method would detect is indeed a reasonable number. Withdrawal of this rejection is requested in view of the claim amendment and the Declaration Under Rule 132.

The New Rejection of Claims 23-24 under 35 U.S.C. § 112, second paragraph

Claims 23-24 are rejected because the term "higher risk" is a relative term that allegedly renders the claim indefinite. Claims 23-24 have been amended to recite that "the prognosis

indicates that the human has a higher risk of neck lymph node metastasis than a human without the transversion" or "the prognosis indicates that the human has a higher risk of cancer recurrence than a human without the transversion." It is respectfully submitted that by inserting the reference to the human without the transversion, the relative term has become definite.

Withdrawal of this rejection is respectfully requested in view of the amendment.

The Rejection of Claims 1-10 and 23-24 under 35 U.S.C. § 112, first paragraph

Claims 1-10 and 23-24 are rejected as not enabled for their full scope. The Office Action posits that the method is enabled for papillary thyroid neoplasms but not for any thyroid neoplasms. The Office Action refers to Table 1, as disclosing that papillary, but not other morphologies of thyroid tumors have BRAF mutations. Applicants now amend Table 1 to correct the formatting errors. Indeed, as the Office Action correctly asserted, amended Table 1 clearly indicates that *BRAF* mutations were found in papillary thyroid tumors (including classic, follicular variant and tall cell variant) but not in Follicular cancer, Hurthle cell cancer, medullary cancer, or benign thyroid neoplasms. To reflect these observations, claim 1 is now amended to specify that the thyroid samples being tested are papillary thyroid tumors. Claim 10 is now amended to reflect that a *BRAF* mutation detected in the blood of a human suspected of having a thyroid neoplasm indicates a malignant papillary thyroid neoplasm.

It is respectfully submitted that independent claims 1 and 10 and dependent claims 2-9 and 23-24 are now commensurate with the scope of enablement. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 6 and 23-24 under 35 U.S.C. § 112, first paragraph

Claims 6 and 23-24 are rejected as not enabled for providing a prognosis based on the presence or absence of the transversion. This rejection is respectfully traversed.

The Office Action alleges that one of skill in the art could not predict that the invention would function as claimed, despite the data which are provided in the specification. The Office Action asserts that the Namba study which did not show a significant correlation between *BRAF* mutation status and either lymph node metastases or cancer recurrence renders the teaching of

the present invention unreliable. This rejection is respectfully traversed.

Subsequent publications on this issue demonstrate that the teachings of the specification are in fact correct and widely applicable. Xing *et al.* report the results of a larger study involving 219 Papillary Thyroid Cancer (PTC) patients. *J. Clin. Endocrin. Metab. 90:*6373-6379, 2005 (Appendix 1). The patients were contributed by multiple centers in multiple countries. See Table 1. A significant association was observed between *BRAF* mutation status and each of lymph node metastases and tumor recurrence. See Table 2. "In patients with PTC, *BRAF* mutation is associated with poorer clinicopathological outcomes and independently predicts recurrence." *Id.* at page 6373. Xing *et al.* conclude, "Importantly, logistic regression adjusting for all the clinical and pathological confounding factors, including PTC subtypes, still showed an independent association of *BRAF* mutation with tumor recurrence and a lower probability of recurrence-free survival, demonstrating the incremental information provided by *BRAF* mutation status in predicting the clinical course of patients with PTC." *Id.* at page 6378.

Xing *et al.* address the very issue raised by the Patent Office: "Controversy has existed among previous reports regarding the association of *BRAF* mutation with high-risk features of PTC." *Ibid.* Xing *et al.* posits the solution to the controversy resides in careful statistical analysis and removal of confounding factors. "Multivariate analyses in our present study suggest that, in addition to differences in sample sizes, confounding risk factors involved, particularly different compositions of PTC subtypes, may well explain these inconsistent findings regarding the relationship of *BRAF* mutation with clinicopathological features in previous studies, which uniformly lacked adjustment for these confounding factors." *Ibid.* Xing *et al.* conclude, "Therefore, *BRAF* mutation is a novel prognostic marker that complements traditionally used prognostic factors for PTC." *Ibid.* This study was published in *Journal of Clinical Endocrinology & Metabolism*, a peer-reviewed journal of The Endocrine Society.

In addition, Vasko *et al.* traced *BRAF* mutations from primary thyroid tumors to lymph node metastases. *J. Clin. Endocrin. Metab. 90:*5265-5269, 2005 (Appendix 2). Vasko *et al.* concluded that "the high prevalence of *BRAF* mutation in lymph node-metastasized thyroid tumors in the cases that harbored this mutation in their primary tumors supports the notion that *BRAF* mutation may facilitate the seeding and progression of PTC cells in lymph nodes, consistent with the finding that *BRAF* mutation was associated with a higher prevalence of

lymph node metastasis of PTC." *Id.* at page 5298.

Thus a larger study and careful statistical analysis confirm the teachings of the present application. Further genetic analysis of lymph node metastases also is consistent with and supports a role of *BRAF* in facilitating metastasis and progression of PTC. These additional data rebut the basis of the rejection. Based on the additional evidence now of record, the method of claims 6 and 23-24 is enabled. Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 1, 3, 4, and 9 under 35 U.S.C. § 102(a)

Claims 1, 3, 4, and 9 stand rejected as anticipated by Kimura et al. (April 1, 2003, Cancer Research 63:1454-1457). The date of this publication precedes applicants' priority date of April 12, 2003 by eleven days.

Section 102 (a) of 35 U.S.C. provides that "[a] person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent."

Applicants submit herewith a Declaration Under Rule 131 which demonstrates that they had conceived of and reduced to practice the claimed invention prior to April 1, 2003, the publication date of the cited reference. Kimura et al. does not qualify as prior art under § 102(a) because it was not published prior to the invention by the applicants.

Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2, 5, and 7 under 35 U.S.C. § 103(a)

Claims 2, 5, and 7 stand rejected as obvious over Kimura *et al.* (*supra)* in view of Tyler et al. (1994, *Surgery 116:*1054-60, abstract only). Tyler is cited for teaching "that fine needle aspirates are used for thyroid cancer diagnosis, that the majority of invasive cancers are found in patients whose lesions are suspicious for papillary carcinoma, and that the risk of carcinoma in these subgroups warrants early surgical intervention."

As discussed above, Kimura does not qualify under §102(a) as prior art because it was published after the applicants made their invention. See Declaration Under Rule 131. Tyler on its own is not sufficient to render the present invention obvious. Tyler does not teach all

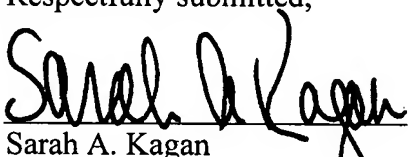
elements of the claimed invention. Particularly, Tyler does not teach a method for distinguishing malignant from benign thyroid samples based on a T → A transversion at nucleotide 1796 of *BRAF*. Because Kimura is not prior art and because Tyler does not teach all elements of the invention, the rejection does not make a *prima facie* case of obviousness.

Withdrawal of this rejection is therefore respectfully requested.

A speedy allowance of all claims is respectfully requested.

Respectfully submitted,

Dated: April 13, 2007

By: 

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